(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 September 2001 (07.09.2001)

PCT

(10) International Publication Number
WO 01/64275 A1

(51) International Patent Classification[7]: A61M 15/00, B65D 83/14

(21) International Application Number: PCT/EP01/02215

(22) International Filing Date: 28 February 2001 (28.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0004763.9	1 March 2000 (01.03.2000)	GB
0018652.8	28 July 2000 (28.07.2000)	GB
0018625.4	28 July 2000 (28.07.2000)	GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HAILEY, Mark, Andrew** [GB/GB]; Glaxo Wellcome plc, Park Road, Ware, Hertfordshire SG12 ODJ (GB). **OTTOLANGUI, David, Michael** [GB/GB]; Glaxo Wellcome plc, Park Street, Ware, Hertfordshire SG12 0DP (GB).

(74) Agent: **CRAWLEY, Karen**; GlaxoSmithKline, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex, TW8 9EP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/64275 A1

(54) Title: METERED DOSE INHALER

(57) Abstract: There is provided according to the invention a component or accessory for use in a metered dose inhaler for dispensing a medicament in a fluid propellant, the component or accessory having a medicament interface comprising a treated surface and an untreated surface. There are also provided processes for its preparation and its use in therapy.

METERED DOSE INHALER

The present invention relates to metered dose inhalers. More especially, the invention relates to a metered dose inhaler for dispensing a suspension or solution comprising a medicament in a liquid propellant, and to components and accessories therefor.

Drugs for treating respiratory and nasal disorders are frequently administered in aerosol formulations through the mouth or nose. One widely used method for dispensing such aerosol drug formulations involves formulating the drug as a suspension or a solution in a liquefied gas propellant. The suspension/solution is stored in a sealed canister capable of withstanding the pressure required to maintain the propellant as a liquid. The suspension/solution is dispersed by activation of a dose metering valve affixed to the canister.

A metering valve generally comprises a metering chamber which is of a set volume and is designed to administer per actuation an accurate predetermined dose of medicament. As the suspension is forced from the canister through the dose metering valve by the high vapour pressure of the propellant, the propellant rapidly vaporizes leaving a fast moving cloud of very fine particles of the drug formulation. This cloud of particles is directed into the nose or mouth of the patient by a channeling device such as a cylinder or open-ended cone. Concurrently with the activation of the aerosol dose metering valve, the patient inhales the drug particles into the lungs or nasal cavity. Systems of dispensing drugs in this way are known as "metered dose inhalers" (MDI's). See Peter Byron, Respiratory Drug Delivery, CRC Press, Boca Raton, FL (1990) for a general background on this form of therapy.

Patients often rely on medication delivered by MDI's for rapid treatment of respiratory disorders which are debilitating and in some cases even life threatening. Therefore, it is essential that the prescribed dose of aerosol medication delivered to the patient consistently meet the specifications claimed by the manufacturer and comply with the requirements of the FDA and other regulatory authorities. That is, every dose dispensed from the can must be the same within close tolerances.

A problem which can exist with drug delivery devices such as MDI's is the deposition of the medicament, or the solid component from a suspension of a particulate product in a liquid propellant, onto the internal surfaces of the device which occurs after a number of operation

cycles and/or storage. This can lead to a reduction in the efficacy of the device and of the resulting treatment as the deposition of the product reduces the amount of active drug available to be dispensed to the patient and markedly reduces the uniformity of the dose dispensed during the lifetime of the device.

The problem of drug adherence and dose uniformity can be greater with hydrofluoroalkane propellants, for example, 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-n-heptafluoropropane (HFA227) which have been developed as ozone friendly replacements of chlorofluorocarbons such as P11, P114 and P12.

Some prior art devices rely on the dispenser being shaken so as to agitate the liquid propellant and product mixture therein, in an attempt to dislodge the deposited particles. However, while in some cases this remedy can be effective within the body of the drug container itself, it may not be effective for particles deposited on the inner surfaces of other MDI components such as the metering valve.

UK patent application no. GB-A-2,328,932 discloses the use of a liner of a material such as fluoropolymer, ceramic or glass to line a portion of the wall of the metering chamber in a metering valve of an MDI. Although this alleviates the problem of deposition in these types of dispensers, it does require the re-design or modification of mouldings and mould tools for producing the valve members to allow for insertion of the liner.

Canadian patent application 2130867 describes a metered dose inhaler containing an aerosol formulation in which the internal walls of the canister are coated with a cross-linked plastics coating. Polytetrafluoroethylene (PTFE) and perfluoroethylenepropylene (FEP) are specifically mentioned as suitable coating materials. International patent application PCT/US96/05005 (WO96/32150) describes a metered dose inhaler in which part or all of the internal surfaces of the canister are coated with a cross-linked polymeric composition, particularly polymer blends comprising one or more fluorocarbon polymers in combination with one or more non-fluorocarbon polymers.

In a co-pending patent application, the inventors disclose MDI's, their components, and accessories treated with a linear, non-cross-linked polymeric composition which provides greater dose uniformity from first to last dose of medicament from an MDI.

The present invention discloses MDI's, and their components and accessories, wherein the pattern of coating or treatment advantageously reduces drug deposition onto the walls of the components and/or affords greater dose uniformity over the lifetime of the device.

Accordingly, in one aspect, the invention provides a component or accessory for use in a metered dose inhaler for dispensing a medicament in a fluid propellant, the component or accessory having a medicament interface comprising a treated surface and an untreated surface.

As used herein, a "medicament interface" means an internal surface of the component or accessory, which is in contact with the medicament during storage and/or dispensing, and is particularly sensitive to medicament deposition during storage and/or dispensing of the medicament.

The term "treated surface" is used herein to indicate a surface which has been altered, e.g. chemically or physically to reduce deposition thereon of the medicament, during storage and/or dispensing. Such alteration may be conducted before, during, or after assembly of the component/accessory material into the component or accessory. Conversely, "untreated surface" is used herein to indicate a surface which has not been altered, e.g. chemically or physically to reduce deposition thereon of the medicament, during storage and/or dispensing.

"Metered dose inhaler" or "MDI" means a unit comprising a canister, a cap covering the mouth of the canister, a drug metering valve situated in the cap, a metering chamber and a suitable channeling device into which the canister is fitted. The term "drug metering valve" or "MDI valve" refers to a valve and its associated mechanisms which delivers a predetermined amount of drug formulation from an MDI upon each activation. The channeling device may comprise, for example, an actuating device for the valve and a cylindrical or cone-like passage through which medicament may be delivered from the filled MDI can via the MDI valve to the nose or mouth of a patient, e.g. a mouthpiece actuator. The relation of the parts of a typical MDI is illustrated in US Patent 5,261,538.

Therefore, a component or accessory may include a canister, and/or a metering valve, and/or a metering chamber, and/or a channeling device and/or an actuator.

The products according to the present invention reduce the variation in dosage with respect to a conventional polymer coated metered dose inhaler.

Preferably, the metered dose inhaler is suitable for consistently dispensing a dose of medicament ranging between 90% and 110% of a prescribed single dosage. Typically, the metered dose inhaler is suitable for dispensing a dose of medicament ranging between 95% and 105% of a prescribed single dosage, for example, 97% and 103%, e.g. 98% and 102%.

Mean dose is calculated by taking ten metered dose inhalers. The beginning of use (BOU) dose and the end of use (EOU) dose is measured for each of the ten inhalers. The mean of the 20 measurements is then calculated. The dosing consistency is calculated by looking at the dose from BOU to EOU and quoting the mean result from each of the 10 determinations as a percentage of the overall mean.

As used herein, "consistently dispensing" defines the dose uniformity of the aerosol medication dispensed to the patient from the first dose through to the final dose dispensed from a drug canister in the MDI device.

In one embodiment, the invention provides a component or accessory for use in a metered dose inhaler, wherein deposition of the medicament during storage and/or dispensing, is substantially or completely alleviated.

In another embodiment, the invention provides a component or accessory for use in a metered dose inhaler, wherein deposition of the medicament during storage and/or dispensing is reduced by between 30% and 80%. Preferably, the deposition is reduced by between 40% and 80%, for example, 40 and 60%, e.g. about 50%.

As used herein, the reference to the "reduction in deposition" of medicament is with respect to the deposition that would occur on a component or accessory wherein the medicament interface is not treated in any way to reduce deposition of the medicament to that surface.

The canister may contain a pharmaceutical aerosol formulation comprising a medicament and a fluorocarbon propellant.

Aerosol formulations which are generally used comprise a suspension of medicament, one or more liquid propellants, optionally with co-propellants and optionally an adjuvant or a surfactant.

Preferably, the contact angle of the treated surface is greater than 70 degrees, for example greater than 90 degrees, e.g. greater than 110 degrees.

As used herein, "contact angle" is identified as the angle between a liquid water droplet and a solid surface at the liquid/solid gas interface.

Typically, the conductivity of the treated surface is greater than 2.4mS, for example, greater than 4.0mS. Preferably, the conductivity is greater than 7.9mS.

As used herein, "conductivity" is evaluated by applying a low voltage of 6.3V between the treated surface and a salt (e.g. 1% sodium chloride) solution alongside the surface, using a WACO™ Enamel Rater II Balance, i.e. using the WACO Conductivity Test for the Determination of Coating Integrity of Metered Dose Inhalers. Therefore, measurements according to this apparatus are greater than 15mA, typically greater than 25mA, e.g. greater than 50mA, which corresponds to a conductivity of greater than 2.4mS, 4.0mS and 7.9mS respectively.

In one embodiment, the treated surface has one or more cross-linked fluorinated polymers disposed thereon, for example, one or more fluorocarbon polymers disposed thereon. Preferably, the treated surface has one or more fluorocarbon polymers in combination with one or more non-fluorocarbon polymers disposed thereon.

In another embodiment, the treated surface has a linear, non-cross-linked polymeric compound disposed thereon.

Typically, the polymeric compound is disposed as a multi-molecular layer thereon, which may be applied as separate layers wherein the layers need not be of the same compound. Alternatively, the polymeric compound is disposed as a mono-molecular layer thereon.

Preferably, the polymeric compound is a fluorocarbon. In particular, the fluorocarbon is highly fluorinated, e.g. has a high fluorine to carbon ratio.

Polymeric compounds will generally be employed as mixtures, the nature of which may be varied as part of optimisation of the employment of the invention.

Preferably, the polymeric compound comprises a functional grouping which is capable of anchoring the compound to the surface of the substrate (e.g. component).

For example, in a first embodiment the compound may be an organo-phosphate such as a phosphate based perfluoroether derivative. Typically, the compound is a phosphoric ester.

In one first such embodiment, the treated surface has a compound disposed thereon having the general formula (I):

$$R^1 - (OC_3F_6)_x - (OCF_2)_y - R^2 \quad (I)$$

wherein R^1 comprises a fluoro-alkyl functional group;
x and y are such that the molecular weight of the compound is 350-1000; and
R^2 comprises a phosphoric ester functional group.

In a second such embodiment, the treated surface has a compound disposed thereon having the general formula (II):

$$R^1 - (CH_2)_v\text{-}CF_2O\text{-}(C_2F_4O)_x - (CF_2O)_yCF_2\text{-}(CH_2)_w - R^1 \quad (II)$$

wherein R^1 comprises:

$-(OCH_2\text{-}CH_2)_z\text{-}OPO(OH)_2$, wherein x, y and z are such that the molecular weight of the compound is 900-2100 and v and w independently represent 1 or 2.

In one preferred embodiment, v and w are both 1. In a second preferred embodiment v and w are both 2.

Alternatively in a second embodiment the compound may be an organo-silane derivative such as a silane derivative of perfluoropolyoxyalkane e.g. a silane derivative of perfluoropolyoxyalkane having a molecular weight in the range 1600-1750. Examples include perfluoropolyethers having functional groups of the type $-CONR^2R^3$ wherein R^2 and R^3 may be independently selected from hydrogen, or a silyl ether ether (e.g. $SiR_t(OR)_{3-t}$

wherein R= hydrogen or C_{1-8} alkyl and t=0 to 2) as disclosed in US Patent 4 746 550 which is incorporated herein by reference.

The synthesis of compounds of formula (I) and (II) may readily be determined by reference to EP 687 533 which describes similar compounds. EP 338 531 also provides information on the preparation of compounds of this type. Methods of preparing other polymeric compounds of the type described above may readily be determined by reference the aforementioned US Patent 4 746 550.

Whilst not being wishing to be bound by any theory, it is believed that the phosphate or silane moiety of the compounds reacts with the surface of the component to anchor the compound to the surface. Thus, when in use, the per-fluorinated end of the compound is presented to the pharmaceutical formulation and so provides a highly fluorinated surface.

The treated surface may be a metallic, metal alloy or plastics surface. Preferably, the treated surface is a metallic or metal alloy surface.

In a first preferred embodiment, the component or accessory having a medicament interface comprising a treated surface and an untreated surface according to the invention is a canister. In a second preferred embodiment the component or accessory having a medicament interface comprising a treated surface and an untreated surface according to the invention is a metering valve, especially a metering chamber.

10-95% of the of the medicament interface of the metered dose inhaler, accessory or component thereof, may be treated, for example, 20-95%, 30-95%, 40-95%, 50-95%, 60-95%, 70-95% or 80-95% of the interface.

Preferably, 40%-95% of the medicament interface thereof is treated, for example, 60%-85%, e.g. about 75%.

The treated surface may define regions and/or patterns on the medicament interface, for example, the defined regions or patterns may take the form of bands, patches, stripes, islands or segments.

In one embodiment, the internal surface of a canister is treated on all sides excluding the base, or lowermost region, of the canister.

In another aspect, the invention provides a metered dose inhaler comprising a canister, and/or a metering valve, and/or a metering chamber, and/or a channeling device and/or an actuator as described hereinabove.

In still another aspect, the invention provides the use of a component or accessory as described above, for dispensing a pharmaceutical aerosol formulation comprising a medicament and a fluorocarbon propellant.

In yet another aspect, the invention provides a process for obtaining a component or accessory as defined above, comprising the step of treating the medicament interface such that during storage and/or dispensing, the medicament is simultaneously in contact with treated and untreated surfaces thereof.

The medicament interface may be coated with one or more cross-linked fluorinated polymers e.g. fluorocarbon polymers. Preferably, the medicament interface is coated with one or more fluorocarbon polymers in combination with one or more non-fluorocarbon polymers.

The term "fluorocarbon polymer" means a polymer in which one or more of the hydrogen atoms of the hydrocarbon chain have been replaced by fluorine atoms. Thus, "fluorocarbon polymers" include perfluorocarbon, hydrofluorocarbon, chlorofluorocarbon, hydrochlorofluorocarbon polymers or other halogen substituted derivatives thereof. The "fluorocarbon polymers" may be branched homo-polymers or co-polymers.

Fluorocarbon polymers for use in the invention include fluorocarbon polymers which are made of multiples of one or more of the following monomeric units: tetrafluorethylene (PTFE), fluorinated ethylene propylene (FEP), perfluoroalkane (PFA), ethylene tetrafluoroethylene (ETFE), vinyldienefluoride (PVDF), and chlorinated ethylene tetrafluorethylene. Fluorinated polymers which have a relatively high ratio of fluorine to carbon, such as perfluorocarbon polymers e.g. PTFE, PFA, and FEP, are preferred.
The fluorinated polymer may be blended with non-fluorinated polymers such as polyamides, polyimides, polyamideimides, polyethersulphones, polyphenylene sulphides, and amine-

formaldehyde thermosetting resins. These added polymers improve adhesion of the polymer coating to the can walls. Preferred polymer blends are PTFE/FEP/polyamideimide, PTFE/polyethersulphone (PES) and FEP-benzoguanamine.

Particularly preferred coatings are pure PFA, FEP and blends of PTFE and polyethersulphone.

Fluorocarbon polymers are marketed under trademarks such as Teflon, Tefel, Halar, Hostaflon, Polyflon, and Neoflon. Grades of polymer include FEP DuPont 856-200, PFA DuPont 857-200, PTFE-PES DuPont 3200-100, PTFE-FEP-polyamideimide DuPont 856P23485, FEP powder DuPont 532, and PFA Hoechst 6900n. The coating thickness is in the range of about 1μm to about 100μm, e.g. 1μm to 25μm. Coatings may be applied in one or more coats.

In another embodiment, the medicament interface is treated with a linear, non-cross-linked polymeric compound.

Preferably, the medicament interface is treated to form a multi-molecular layer thereon, which may be applied as separate layers wherein the layers need not be the same compound. Most preferably, the medicament interface is treated to form a mono-molecular layer thereon.

In a preferred embodiment, the polymeric compound is a fluorocarbon. Preferably, the compound is highly fluorinated.

Typically, the linear, non-cross-linked polymeric compound comprises a functional grouping which is capable of anchoring the compound to the surface to be treated.

In a first embodiment, preferably, the compound is an organo-phosphate, for example, a phosphate based perfluoroether derivative. Typically, the compound takes the form of a phosphoric ester.

In one first such embodiment, the medicament interface is treated with a compound having the general formula (I) as described above. In a second such embodiment, the medicament interface is treated with a compound having the general formula (II) as described above.

In a second embodiment, preferably the compound is an organo-silane derivative such as a silane derivative of perfluoropolyoxyalkane. More preferably, the medicament interface is treated with a compound which is a silane derivative of perfluoropolyoxyalkane having a molecular weight in the range 1600-1750.

The applicants also contemplate that the manufacturing machinery used to produce MDI's, their components and accessories may also be treated in accordance with the invention. Furthermore, apparatus for filling empty canisters, or other MDI components, with medicament may also be treated. In this way, inaccuracies due to deposition or drug metering may be prevented at the stage of loading the MDI with its quota of medicament. The metered dose inhalers may be prepared by methods of the art (e.g. see Byron above and US patent 5,345,980) substituting conventional cans for those treated in accordance with the present invention.

Conventionally, the canisters and caps for use in MDI's are made of aluminium or an alloy of aluminium although other metals not affected by the drug formulation, such as stainless steel, an alloy of copper, or tin plate, may be used. An MDI canister may also be fabricated from glass or plastic. The MDI canisters and caps employed are preferably made of aluminium or an alloy thereof.

The drug metering valve may consist of parts usually made of stainless steel, a pharmacologically resilient polymer, such as acetal, polyamide (e.g. Nylon^{R}), polycarbonate, polyester, fluorocarbon polymer (e.g. Teflon^{R}) or a combination of these materials. Additionally, seals and "O" rings of various materials (e.g., nitrile rubbers, polyurethane, acetyl resin, fluorocarbon polymers), or other elastomeric materials are employed in and around the valve.

The components of the MDI described hereinabove may be pretreated as coil stock, such as aluminium or stainless steel, e.g by applying the coating (e.g. by spraying) in defined regions of the sheet metal in a pattern such as bands, patches, stripes islands or segments before it is stamped or drawn into shape. This method is well suited to high volume production due to the high standards of uniformity that can be achieved and to the high speed and precision with which pre-coated stock can be drawn or stamped.

Alternative the regions of the surface which are to remain untreated may require masking with a material which prevents the surface being coated during the treating process e.g spraying the coating solution onto the surface or dipping the surface into a tank containing the coating solution. This material will usually require removing after part or all of the treatment process is complete. A suitable material for masking the surface may be liquid that is immiscible with the solution of the coating used in the treating process. Alternatively the masking material may be a physical barrier such as a removable plastic film or waxy paper layer.

Alternatively, the components may be manufactured according to a second process comprising treating pre-formed canisters. The masking methods described above may be suitable for providing untreated regions of surface area.

For a treatment comprising fluorocarbon polymer coating, it is preferred to use MDI canisters and other components made of aluminium or an alloy thereof. Advantageously, strengthened aluminium or aluminium alloy MDI components may be employed. Such strengthened MDI components are capable of withstanding particularly stressful coating and curing conditions e.g. particularly high temperatures, which may be required for certain fluorocarbon polymers. Strengthened MDI components which have a reduced tendency to malform under high temperatures include MDI canisters comprising a substantially ellipsoidal base (which increases the angle between the side walls and the base of the canister), rather than the hemispherical base of standard MDI canisters. MDI canisters having an ellipsoidal base offer the further advantage of facilitating the coating process.

Other techniques for obtaining treated components include electrostatic dry powdered coating or by spraying pre-formed MDI components inside with formulations of the fluorinated polymer/polymer blend and then curing. Pre-formed components may also be dipped in formulation and then cured.

Wherein the complete surface of the material (e.g. sheet metal) or canister is treated then it may be appropriate to remove parts of the coating for example using abrasive means.

The fluorocarbon polymer/polymer blend may also be formed in situ at the MDI component surface using plasma polymerization of the fluorocarbon monomers. Fluorocarbon polymer

film may be blown onto components as many fluorocarbon polymers are available as film stock.

For polymeric coatings, the appropriate curing temperature is dependent on the fluorocarbon polymer/polymer blend chosen for the coating and the coating method employed. However, for coil coating and spray coating temperatures in excess of the melting point of the polymer are typically required, for example, about 50C above the melting point for up to 20 minutes such as about 5 to 10 minutes e.g. about 8 minutes or as required. For the above named preferred and particularly preferred fluorocarbon polymer/polymer blends curing temperatures in the range of about 300 to about 400°C e.g. about 350°C to 380°C are suitable. For plasma polymerization, typically temperatures in the range of about 20 to 100°C may be employed.

The components or coil stock may be dipped or bath immersed into a treatment tank containing a solution of cross-linked polymeric or non-cross-linked polymeric composition.

For the non-cross-linked polymeric treatment, the components or coil stock may be treated with 0.1 to 10% w/w, preferably 0.5 to 5%, especially about 1%, solution of a non-cross-linked polymeric compound as described above or a mixture thereof in any suitable solvent such as isopropyl alcohol.

Preferably, the pre-formed components or the coil stock are immersed in a non-cross-linked polymeric solution at room temperature for at least one hour, e.g. 12 hours. The non-polymer treated components are preferably washed with solvent and dried at an elevated temperature for example 50-100°C optionally under vacuum.

The MDI components taught herein may be used in medical practice in a similar manner as non-coated MDI components. However, the components taught herein are particularly useful for containing and dispensing inhaled drug formulations with hydrofluoroalkane fluorocarbon propellants such as 134a with little, or essentially no, excipient and which tend to deposit or cling to interior walls and part of the MDI system. In certain cases it is advantageous to dispense an inhalation drug with essentially no excipient e.g. where the patient may be allergic to an excipient or the drug reacts with an excipient.

Further aspects of the invention provide the use of MDI's and the components for use in MDI's described above for the treatment of respiratory disorders e.g. asthma.

In medical use the canisters in accordance with the invention contain a pharmaceutical aerosol formulation comprising a medicament and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant.

Suitable propellants include, for example, C_{1-4}hydrogen-containing chlorofluorocarbons such as CH_2ClF, $CClF_2CHClF$, CF_3CHClF, CHF_2CClF_2, $CHClFCHF_2$, CF_3CH_2Cl and $CClF_2CH_3$; C_{1-4}hydrogen-containing fluorocarbons such as CHF_2CHF_2, CF_3CH_2F, CHF_2CH_3 and CF_3CHFCF_3; and perfluorocarbons such as CF_3CF_3 and $CF_3CF_2CF_3$.

Where mixtures of the fluorocarbons or hydrogen-containing chlorofluorocarbons are employed they may be mixtures of the above identified compounds or mixtures, preferably binary mixtures, with other fluorocarbons or hydrogen-containing chloro- fluorocarbons for example $CHClF_2$, CH_2F_2 and CF_3CH_3. Preferably a single fluorocarbon or hydrogen-containing chlorofluorocarbon is employed as the propellant. Particularly preferred as propellants are C_{1-4}hydrogen-containing fluorocarbons such as 1,1,1,2-tetrafluoroethane(CF_3CH_2F) and 1,1,1,2,3,3,3-heptafluoro-n-propane (CF_3CHFCF_3) or mixtures thereof. 1,1,1,2-Tetrafluoroethane is of particular interest.

The pharmaceutical formulations for use in the canisters of the invention contain no components which provoke the degradation of stratospheric ozone. In particular the formulations are substantially free of chlorofluorocarbons such as CCl_3F, CCl_2F_2 and CF_3CCl_3.

The propellant may additionally contain a volatile adjuvant such as a saturated hydrocarbon for example propane, n-butane, isobutane, pentane and isopentane or a dialkyl ether for example dimethyl ether. In general, up to 50% w/w of the propellant may comprise a volatile hydrocarbon, for example 1 to 30% w/w. However, formulations which are free or substantially free of volatile adjuvants are preferred. In certain cases, it may be desirable to include appropriate amounts of water, which can be advantageous in modifying the dielectric properties of the propellant.

A polar co-solvent such as C_{2-6} aliphatic alcohols and polyols e.g. ethanol, isopropanol and propylene glycol, preferably ethanol, may be included in the drug formulation in the desired amount to improve the dispersion of the formulation, either as the only excipient or in addition to other excipients such as surfactants. Suitably, the drug formulation may contain 0.01 to 5% w/w based on the propellant of a polar co-solvent e.g. ethanol, preferably 0.1 to 5% w/w e.g. about 0.1 to 1% w/w.

A surfactant may also be employed in the aerosol formulation. Examples of conventional surfactants are disclosed in EP 372777 incorporated herein by reference. The amount of surfactant employed is desirable in the range 0.0001% to 50% weight to weight ratio relative to the medicament, in particular, 0.05 to 5% weight to weight ratio. Preferred surfactants are lecithin, oleic acid and sorbitan trioleate. Preferred formulations, however, are free or substantially free of surfactant.

Pharmaceutical formulations may contain 0.0001 to 50% w/w, preferably 0.001 to 20%, for example 0.001 to 1% of sugar relative to the total weight of the formulation. Generally the ratio of medicament to sugar falls within the range of 1:0.01 to 1:100 preferably 1:0.1 to 1:10. Typical sugars which may be used in the formulations include, for example, sucrose, lactose and dextrose, preferably lactose, and reducing sugars such as mannitol and sorbitol, and may be in micronised or milled form.

The final aerosol formulation desirably contains 0.005-10% w/w, preferably 0.005 to 5% w/w, especially 0.01 to 1.0% w/w, of medicament relative to the total weight of the formulation.

Medicaments which may be administered in aerosol formulations according to the invention include any drug useful in inhalation therapy and which may be presented in a form which is substantially completely insoluble in the selected propellant. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; anti-allergics, e.g. cromoglycate (e.g. as sodium salt), ketotifen or nedocromil (e.g. as sodium salt); antiinfectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; anti-histamines, e.g. methapyrilene; anti-inflammatories, e.g. beclomethasone (e.g. as dipropionate), fluticasone (e.g. as propionate), flunisolide, budesonide, rofleponide, mometasone (e.g. as furoate), ciclesonide, triamcinolone (e.g. as acetonide) or 6α, 9α-

difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester; anti-tussives, e.g. noscapine; bronchodilators, e.g. albuterol (e.g. as free base or as sulphate), salmeterol (e.g. as xinafoate), ephedrine, adrenaline, fenoterol (e.g. as hydrobromide), formoterol (e.g. as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (e.g. as acetate), reproterol (e.g. as hydrochloride), rimiterol, terbutaline (e.g. as sulphate), isoetharine, tulobuterol, 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]amino]-ethyl-2(3H)-benzothia-zolone; diuretics, e.g. amiloride; anti-cholinergics, e.g. ipratropium (e.g. as bromide), tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant. It will further be clear to a person skilled in the art that where appropriate, the medicaments may be used in the form of a pure isomer, for example, R-albuterol or RR-formoterol.

Particularly preferred medicaments for administration using aerosol formulations in accordance with the invention include anti-allergics, bronchodilators and anti-inflammatory steroids of use in the treatment of respiratory disorders such as asthma by inhalation therapy, for example cromoglycate (e.g. as the sodium salt), salbutamol (e.g. as the free base or the sulphate salt), salmeterol (e.g. as the xinafoate salt), formoterol (e.g. as the fumarate salt), terbutaline (e.g. as the sulphate salt), reproterol (e.g. as the hydrochloride salt), a beclomethasone ester (e.g. the diproprionate), a fluticasone ester (e.g. the propionate). Salmeterol, especially salmeterol xinafoate, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof are especially preferred.

It will be appreciated by those skilled in the art that the aerosol formulations according to the invention may, if desired, contain a combination of two or more active ingredients. Aerosol compositions containing two active ingredients are known for the treatment of respiratory disorders such as asthma, for example, formoterol and budesonide, salmeterol (e.g. as the xinafoate salt) and fluticasone (e.g. as the propionate ester), salbutamol and beclomethasone (as the dipropionate ester) are preferred.

A particularly preferred combination is a combination of fluticasone propionate and salmeterol, or a salt thereof (particularly the xinafoate salt).

Particularly preferred formulations for use in the canisters of the present invention comprise a medicament and a C_{1-4} hydrofluoroalkane particularly 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-n-heptafluoropropane or a mixture thereof as propellant.

Preferred formulations are free or substantially free of formulation excipients. Thus, preferred formulations consist essentially of (or consist of) the medicament and the selected propellant.

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method a metering valve is crimped onto an aluminium can to form an empty canister. The particulate medicament is added to a charge vessel and liquified propellant is pressure filled through the charge vessel into a manufacturing vessel. The drug suspension is mixed before re-circulation to a filling machine and an aliquot of the drug suspension is then filled through the metering valve into the canister.

In an alternative process, an aliquot of the liquefied formulation is added to an open canister under conditions which are sufficiently cold such that the formulation does not vaporise, and then a metering valve crimped onto the canister.

Preferably the canister is fitted with a cap assembly, wherein a formulation metering valve is situated in the cap, and said cap is crimped in place. The cap may be secured onto the canister via welding such as ultrasonic welding or laser welding, screw fitting or crimping. MDIs taught herein may be prepared by methods of the art (e.g, see Byron, above and WO96/32150) substituting conventional cans for those treated in accordance with the present invention.

Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release testing.

Each filled canister is conveniently fitted into a suitable channeling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs or nasal cavity of a patient. Suitable channeling devices comprise for example a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the nose or mouth of a patient e.g. a mouthpiece actuator. Metered dose inhalers are designed to deliver a fixed unit dosage of medicament per actuation or "puff", for example in the range of 10 to 5000 microgram medicament per puff.

Administration of medicament may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment. It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular particulate medicament used and the frequency of administration and will ultimately be at the discretion of the attendant physician. When combinations of medicaments are employed the dose of each component of the combination will in general be that employed for each component when used alone. Typically, administration may be one or more times, for example from 1 to 8 times per day, giving for example 1,2,3 or 4 puffs each time. Each valve actuation, for example, may deliver 5μg, 50μg, 100μg, 200μg or 250μg of a medicament. Typically, each filled canister for use in a metered dose inhaler contains 60, 100, 120 or 200 metered doses or puffs of medicament; the dosage of each medicament is either known or readily ascertainable by those skilled in the art.

A still further aspect of the present invention comprises a method of treating respiratory disorders such as, for example, asthma, which comprises administration by inhalation of an effective amount of an aerosol formulation as herein described from a metered dose inhaler of the present invention.

Examples

Example 1

Standard 12.5ml MDI canisters (Presspart Inc Cary NC) are stamped/drawn from coil stock pretreated by spraying the surface to form bands with a solution of 1% w/w compound of formula (I) in isopropyl alcohol which was then allowed to dry at 80°C under vacuum. The cans are then purged of air and the valves crimped in place, and a suspension of about 31.8mg salbutamol sulphate in about 19.8g HFA 134a is filled through the valve.

Example 2

Example 1 is repeated except a suspension of about 4.25mg salmeterol xinafoate and about 8g HFA 134a is filled through the valve.

Example 3

Example 1 is repeated except a suspension of 22mg fluticasone propionate and 15g HFA 134a is filled through the valve.

Example 4

Example 1 is repeated except a suspension of about 44mg fluticasone propionate and about 12g HFA 134a is filled through the valve.

Example 5

Example 1 is repeated except a suspension of about 13.8mg fluticasone propionate with about 4mg salmeterol xinafoate and 8 g HFA 134a is filled through the valve.

Example 6

Example 1 is repeated except a suspension of about 29mg fluticasone propionate with about 21.4g HFA 227 is filled through the valve.

Example 7-12

Examples 1 to 6 are repeated except that a compound of formula (II) is employed instead of a compound of formula (I).

Examples 13-18

Examples 1 to 6 are repeated except that a silane derivative of perfluoropolyoxyalkane with a molecular weight in the range 1600-1750 is employed instead of a compound of formula (I).

It will be understood that the present disclosure is for the purpose of illustration only and the invention extends to modifications, variations and improvements thereto which will be within the ordinary skill of the person skilled in the art.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to

the exclusion of any other integer or step or group of integers or steps.

Claims:-

1. A component or accessory for use in a metered dose inhaler for dispensing a medicament in a fluid propellant, the component or accessory having a medicament interface comprising a treated surface and an untreated surface.

2. A component or accessory as claimed in claim 1 selected from the group consisting of a canister, a metering valve, a metering chamber, a channeling device and an actuator for use in a metered dose inhaler.

3. A component or accessory as claimed in claim 1 or claim 2, comprising a canister containing a pharmaceutical aerosol formulation comprising a medicament and a fluorocarbon propellant.

4. A component or accessory as claimed in any one of claims 1 to 3, for consistently dispensing a dose of medicament ranging between 90 and 110% of a prescribed single dosage.

5. A component or accessory as claimed in any one of claims 1 to 4, wherein deposition of the medicament during storage and/or deposition, is substantially or completely alleviated.

6. A component or accessory as claimed in any one of claims 1 to 5, wherein deposition of the medicament during storage and/or deposition is reduced by between 30% and 80%.

7. A component or accessory as claimed in any one of claims 1 to 6, wherein the contact angle of the treated surface is greater than 70 degrees.

8. A component or accessory as claimed in any one of claims 1 to 7, wherein the conductivity of the treated surface is greater than 2.4mS.

9. A component or accessory as claimed in any one of claims 1 to 8, wherein the treated surface has one or more cross-linked fluorinated polymers disposed thereon.

10. A component or accessory as claimed in claim 9 wherein the treated surface has one or more fluorocarbon polymers disposed thereon.

11. A component or accessory as claimed in claim 10 wherein the treated surface has one or more fluorocarbon polymers in combination with one or more non-fluorocarbon polymers disposed thereon.

12. A component or accessory as claimed in any one of claims 1 to 8, wherein the treated surface has a linear, non-cross-linked polymeric compound disposed thereon.

13. A component or accessory as claimed in claim 12 wherein the polymeric compound is disposed as a multi-molecular layer thereon.

14. A component or accessory as claimed in claim 12 wherein the polymeric compound is disposed as a mono-molecular layer thereon.

15. A component or accessory as claimed in any one of claims 12 to 14 wherein the polymeric compound is a fluorocarbon.

16. A component or accessory as claimed in claim 15 wherein the fluorocarbon is highly fluorinated.

17. A component or accessory as claimed in any one of claims 12 to 16 wherein the polymeric compound comprises a functional grouping which is capable of anchoring the compound to the surface thereof.

18. A component or accessory as claimed in claim 17 wherein the compound is an organo-phosphate.

19. A component or accessory as claimed in claim 18 wherein the compound is a phosphate based perfluoroether derivative.

20. A component or accessory as claimed in claim 18 or claim 19 wherein the compound is a phosphoric ester.

21. A component or accessory as claimed in claim 20 wherein the treated surface has a compound disposed thereon having the general formula (I):

$$R^1 - (OC_3F_6)_x - (OCF_2)_y - R^2 \quad (I)$$

wherein R^1 comprises a fluoro-alkyl functional group;
x and y are such that the molecular weight of the compound is 350-1000; and
R^2 comprises a phosphoric ester functional group.

22. A component or accessory as claimed in claim 20 wherein the treated surface has a compound disposed thereon having the general formula (II):

$$R^1 - (CH_2)_v-CF_2O-(C_2F_4O)_x - (CF_2O)_yCF_2-(CH_2)_w- R^1 \quad (II)$$

wherein R^1 comprises:
$-(OCH_2-CH_2)_z-OPO(OH)_2$, wherein x, y and z are such that the molecular weight of the compound is 900-2100 and v and w independently represent 1 or 2.

23. A component or accessory as claimed in claim 22 wherein, v and w are both 1

24. A component or accessory as claimed in claim 22 wherein, v and w are both 2

25. A component or accessory as claimed in claim 17 wherein the compound is an organo-silane derivative.

26. A component or accessory as claimed in claim 25 wherein the compound is a silane derivative of perfluoropolyoxyalkane.

27. A component or accessory as claimed in claim 26 wherein the treated surface has a compound disposed thereon which is a silane derivative of perfluoropolyoxyalkane having a molecular weight in the range 1600-1750.

28. A component or accessory as claimed in any one of claims 1 to 27, wherein the treated surface is a metallic, metal alloy or plastics surface.

29. A component or accessory as claimed in claim 28 wherein the treated surface is a metallic or metal alloy surface.

30. A component or accessory as claimed in any one of claims 1 to 29, wherein 10-95% of the medicament interface thereof is treated.

31. A component or accessory as claimed in any one of claims 1 to 30, wherein the treated surface defines regions and/or patterns on the medicament interface.

32. A component or accessory for use in a metered dose inhaler as claimed in claim 31, wherein the defined regions or patterns take the form of bands, patches, stripes, islands or segments.

33. A metered dose inhaler comprising a canister, and/or a metering valve, and/or a metering chamber, and/or a channeling device and/or an actuator as claimed in any one of claims 2 to 32.

34. Use of a metered dose inhaler as claimed in claim 33 or component or accessory as claimed in any one of claims 1 to 32, for dispensing a pharmaceutical aerosol formulation comprising a medicament, a fluorocarbon propellant and optionally a solvent.

35. Use as claimed in claim 34 wherein the pharmaceutical aerosol formulation to be dispensed is a medicament suspended in propellants selected from liquefied HFA 134a, 227 or a mixture thereof.

36. Use as claimed in claim 34 or 35 wherein the propellant is substantially free of adjuvants.

37. Use as claimed in any one of claims 34 to 36 in which the medicament is selected from fluticasone propionate, salbutamol, beclomethasone dipropionate, salmeterol, pharmaceutically acceptable salts, solvates or esters thereof and mixtures thereof.

38. A process for obtaining a component or accessory as claimed in any one of claims 1 to 33, comprising the step of treating a medicament interface such that during storage

and/or dispensing, the medicament is simultaneously in contact with treated and untreated surfaces thereof.

39. A process as claimed in claim 38 wherein the medicament interface is coated with one or more cross-linked fluorocarbon polymers.

40. A process as claimed in claim 39 wherein the medicament interface is coated with one or more fluorocarbon polymers in combination with one or more non-fluorocarbon polymers.

41. A process as claimed in any one of claims 38 wherein the medicament interface is treated with a linear, non-cross-linked polymeric compound.

42. A process as claimed in claim 39 or claim 41 wherein the medicament interface is treated to form a multi-molecular layer thereon.

43. A process as claimed in claim 39 or claim 41 wherein the medicament interface is treated to form a mono-molecular layer thereon.

44. A process as claimed in any one of claims 41 to 43 wherein the polymeric compound is a fluorocarbon.

45. A process as claimed in claim 44 wherein the compound is highly fluorinated.

46. A process as claimed in any one of claims 41 to 45 wherein the linear, non-cross-linked polymeric compound comprises a functional grouping which is capable of anchoring the compound to the surface to be treated.

47. A process as claimed in claim 46 wherein the polymeric compound is an organo-phosphate

48. A process as claimed in claim 47 wherein the polymeric compound is a phosphate based perfluoroether derivative.

49. A process as claimed in claim 47 or claim 48 wherein the polymeric compound is a phosphoric ester.

50. A process as claimed in any one of claims 41 to 49 wherein the medicament interface is treated with a compound having the general formula (I):

$$R^1 - (OC_3F_6)_x - (OCF_2)_y - R^2 \quad (I)$$

wherein R^1 comprises a fluoro-alkyl functional group;
x and y are such that the molecular weight of the compound is 350-1000; and
R^2 comprises a phosphoric ester functional group.

51. A process as claimed in any one of claims 41 to 49 wherein the medicament interface is treated with a compound having the general formula (II)

$$R^1 - (CH_2)_v-CF_2O-(C_2F_4O)_x - (CF_2O)_yCF_2-(CH_2)_w- R^1 \quad (II)$$

wherein R^1 comprises:
$-(OCH_2-CH_2)_z-OPO(OH)_2$, wherein x, y and z are such that the molecular weight of the compound is 900-2100 and v and w independently represent 1 or 2.

52. A process as claimed in any one of claims 41 to 46 wherein the polymeric compound is an organo-silane derivative.

53. A process as claimed in claim 52 wherein the polymeric compound is a silane derivative of perfluoropolyoxyalkane.

54. A process as claimed in any one of claims 41 to 46, 52 or 53 wherein the medicament interface is treated with a compound which is a silane derivative of perfluoropolyoxyalkane having a molecular weight in the range of 1600-1750.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/02215

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M15/00 B65D83/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M B65D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 32150 A (GLAXO WELLCOME INC ;ASHURST IAN C (US); HERMAN CRAIG S (US); LI LI) 17 October 1996 (1996-10-17) cited in the application page 2, line 24 -page 10, line 26; examples	1-54
Y	WO 98 19727 A (DU PONT) 14 May 1998 (1998-05-14) page 2, line 30 -page 8, line 14; figures	1-54
A	GB 2 328 932 A (BESPAK PLC) 10 March 1999 (1999-03-10) cited in the application page 2, line 12 -page 3, line 17; figures	1-54

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 July 2001	17/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Olsson, B

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

	national Application No
	PCT/EP 01/02215

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 642 992 A (CIBA GEIGY AG) 15 March 1995 (1995-03-15) column 2, line 18 -column 6, line 9; figures	1-54
A	WO 96 32345 A (ASHURST IAN C ;LI LI (US); HERMAN CRAIG S (US); RIEBE MICHAEL T (U) 17 October 1996 (1996-10-17) page 2, line 27 -page 10, line 30; examples	1-54
A	WO 96 32151 A (GLAXO WELLCOME INC ;ASHURST IAN C (GB); HERMAN CRAIG S (US); LI LI) 17 October 1996 (1996-10-17) page 2, line 24 -page 10, line 19; examples	1-54

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/02215

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9632150 A	17-10-1996	AU 718263 B	13-04-2000
		AU 5481196 A	30-10-1996
		BG 102022 A	31-07-1998
		BR 9604977 A	09-06-1998
		CA 2217954 A	17-10-1996
		CN 1186447 A	01-07-1998
		CZ 9703260 A	18-02-1998
		EP 0820323 A	28-01-1998
		HU 9802391 A	01-02-1999
		JP 11509434 T	24-08-1999
		NO 974736 A	11-12-1997
		NZ 306280 A	29-07-1999
		PL 322771 A	16-02-1998
		SK 138997 A	08-04-1998
		TR 9701169 T	21-03-1998
		US 6143277 A	07-11-2000
WO 9819727 A	14-05-1998	AU 5195498 A	29-05-1998
		EP 0942762 A	22-09-1999
GB 2328932 A	10-03-1999	GB 2338951 A,B	12-01-2000
		DE 19835273 A	04-03-1999
		FR 2767801 A	05-03-1999
		FR 2779705 A	17-12-1999
		US 6089256 A	18-07-2000
		US 6095182 A	01-08-2000
EP 0642992 A	15-03-1995	AT 163623 T	15-03-1998
		AU 690913 B	07-05-1998
		AU 7142994 A	09-03-1995
		CA 2130867 A	28-02-1995
		DE 59405357 D	09-04-1998
		DK 642992 T	07-12-1998
		ES 2113074 T	16-04-1998
		GR 3026507 T	31-07-1998
		HK 1010716 A	28-04-2000
		JP 7076380 A	20-03-1995
WO 9632345 A	17-10-1996	AP 835 A	12-05-2000
		AU 718851 B	20-04-2000
		AU 5481296 A	30-10-1996
		BG 102023 A	31-07-1998
		BR 9604979 A	09-06-1998
		CA 2218179 A	17-10-1996
		CN 1186473 A	01-07-1998
		CZ 9703261 A	16-06-1999
		EP 0820414 A	28-01-1998
		HU 9800641 A	28-08-1998
		JP 2000513237 T	10-10-2000
		NO 974738 A	11-12-1997
		NZ 306281 A	29-07-1999
		PL 322781 A	16-02-1998
		SK 139197 A	08-04-1998
		TR 9701170 T	21-02-1998
		US 6149892 A	21-11-2000
WO 9632151 A	17-10-1996	AU 718576 B	13-04-2000
		AU 5390196 A	30-10-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/02215

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9632151 A		BG 101972 A	30-04-1998
		BR 9604978 A	09-06-1998
		CA 2217948 A	17-10-1996
		CZ 9703258 A	18-03-1998
		EP 1084726 A	21-03-2001
		EP 0820322 A	28-01-1998
		HU 9802278 A	28-01-1999
		JP 11503352 T	26-03-1999
		NO 974735 A	11-12-1997
		NZ 305787 A	29-07-1999
		PL 322770 A	16-02-1998
		SK 139097 A	06-05-1998
		TR 9701168 T	21-05-1998